REMARKS/ARGUMENTS

Claims 1 and 24-87 are pending in the above-referenced application.

Claims 31 and 35 have been amended to remove the informalities. Claim 85 has been cancelled. Claims 1 and 34 have been amended to further define Applicant's invention. Claims 70-78 have been amended to address the § 101 rejections although Applicant does not necessarily agree with the conclusion. Claims 24-26, 28-33, 36, 37, 44, 54-56, 59-62, 64, 74, 75 and 82-85 have been amended to satisfy the requirement of § 112, second paragraph. Claims 43, 51, 61, 81 and 87 have been amended to satisfy the requirement of § 112, first paragraph. No new matter has been added.

This is a response to the non-final Office Action dated October 14, 2009 wherein the Examiner objected to claim 85 under 37 CFR 1.75 as being a duplicate of claim 83; and claims 31 and 35 for informalities. The Examiner rejected: (1) claims 70-78 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process; (2) claims 24-26, 28-33, 36, 37, 44, 54-56, 59-62, 64, 74, 75 and 82-85 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention; (3) claims 43, 51, 61, 81 and 87 under 35 U.S.C. 112, first paragraph, for being non-enabling with respect to compositions containing any possible physiological active ingredient; (4) claims 1, 24-34, 42, 43, 52, 60 and 61 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 7,285,661 (Sommermeyer et al.); (5) claims 62-69 under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer in view of U.S. Patent No. 5,218,108 (Sommermeyer et al.); (6) claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57 and 79-87 under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer as applied to claims 1, 24-34, 42, 43, 52, 60 and 61, and further in view of U.S. Patent No. 6,610,294 (Lederman et al.); and (7) claim 59 under 35 U.S.C. 103(a) as being unpatentable over Sommermeyer in view of Lederman as applied to claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57 and 79-97, and further in view of U.S. Patent No. 4,775,638 (Haisma).

Claims 40, 48 and 58 are objected to for depending from a rejected base claim but would be allowable if rewritten in independent form incorporating all the limitations of the rejected base claim and intervening claims.

In view of the amendments set forth above and the remarks that follow, reconsideration of the rejections and a notice of allowance are respectfully solicited.

Claim objections

Claim 85 has been canceled to obviate the duplicity rejection. Claims 31 and 35 have been amended to correct for informalities. In view of the amendments, rescission of the objection is respectfully solicited.

Claims 40, 48 and 58 are objected to for depending from a rejected base claim but would be allowable if rewritten in independent form incorporating all the limitations of the rejected base claim and intervening claims. Applicant respectfully thanks the Examiner for conditionally allowing these claims but will defer amending them at this time with reservation that they may be amended at a future date.

§ 101 Rejection of Claims 70-78

Process claims 70-78 are rejected under 35 U.S.C. 101 for not setting forth any steps involved in the process. Claims 70-78 have been amended as indicated above. In view of the amendments, rescission of the § 101 rejection and reexamination of amended claims 70-78 are respectfully solicited.

§ 112, second paragraph Rejection of Claims 24-26, 28-33, 36, 37, 44, 54, 55, 56, 59, 60, 61, 64, 70-78, and 82-85

Claims 24-26, 28-33, 36, 37, 44, 54, 55, 56, 59, 60, 61, 64, 70-78, and 82-85 are rejected under 35 U.S.C 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The above-

identified claims have been amended as indicated above. In view of the amendments, rescission of the § 112, second paragraph rejection is respectfully solicited.

§ 112, first paragraph Rejection of Claims 43, 51, 61, 81 and 87

Claims 43, 51, 61, 81 and 87 are rejected under 35 U.S.C 112, first paragraph "because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with [the above-identified] claims". Claims 43, 51, 61, 81 and 87 have been amended as indicated above. In view of the amendments, rescission of the § 112, first paragraph rejection is respectfully solicited.

§ 103(a) Rejection of Claims 1, 24-34, 42, 43, 52, 60 and 61 by Sommermeyer

In rejecting claims 1, 24-34, 42, 43, 52 and 60 as being unpatentable over Sommermeyer, the Examiner contends that Sommermeyer discloses conjugates of oxidized substituted or unsubstituted starch radical with drugs. However, Sommermeyer does not specifically disclose starches having the exact molecular weight, degree of substitution, and C2/C6 ratio recited in the instant claims. The Examiner concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the conjugates and compositions of Sommermeyer having the molecular weight, degree of substitution, and C2/C6 ratio recited in the instant claims. The claimed ranges overlap or fall within the ranges disclosed in the prior art. One of ordinary skill in the art would have been able to arrive at the claimed ranges through a process of optimizing these result-effective variables within the broad disclosure of the prior art. (Office Action, page 11)

Of the rejected claims, amended independent claim 1 recites:

> 1. (Currently Amended) A hydroxyethylstarch for use as a volume replacement or plasma expander having an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8.

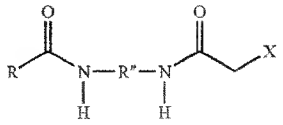
Thus, amended claim 1 is directed to a hydroxyethyl starch for use as a volume replacement or plasma expander having an average molecular weight of greater than or equal to 500,000 characterized by having a C2/C6 ratio of from 2 to below 8.

In contrast, the '661 Sommermeyer patent is directed to the use of starch derivatives in the production of medicaments or drugs. Specifically, the '661 Sommermeyer patent is directed to starch derivatives which can satisfy the following specific criteria:

(1) The starch derivatives can bind selectively to an active substance of interest (Col. 1, lines 61-63);

(2) The starch derivatives are "decomposable without residue within a physiologically reasonable period, but on the other hand exhibit a controllable elimination behavior" (Col. 2, lines 60-63).

To this end, Sommermeyer teaches a starch derivative of formula (I) (reproduced herein), whereby:



(I)

X denotes a bromine or [idodine atom], R'' denotes a straight-chain or branched alkyl, aryl or aralkyl compound and R-CO- denotes an oxidized substituted or unsubstituted starch radical, which is oxidized at the reducing end group to form a carboxylic acid. (Col. 2, lines 35-51).

To obtain a starch derivative of formula (I) which can satisfy the above-identified criteria, Sommermeyer teaches an oxidized "hydroxyethyl starch (HES) radical R-CO- within the formula (I)" having an average molecular weight of 2000 to 1,000,000 Dalton, most preferably 8,000 to 250,000 Dalton (Col. 4, lines 39-44), a molar substitution MS of 0.1 to 0.8, preferably 0.4 to 0.7 (Col. 3, lines 36-39), and a C2/C6 substitution ratio in the range of 2 to 12, preferably from 3 to 11 (Col. 4, lines 1-5). As further discussed below, a HES radical chemically altered to form a starch derivative of formula (I) is different from the hydroxyethylstarch of claim 1 and therefore fails to render the pending claim obvious.

It should be noted that Sommermeyer invariably refers to the above-identified characteristics as pertaining specifically to "a hydroxyethyl starch radical R-CO-within the formula (I)" (Col. 3, line 6; Col. 4, line 2 and line 39). In other words, Sommermeyer makes clear that the disclosed ranges in Molecular weight, molar substitution and C2/C6 substitution ratio are specific for a HES radical chemically altered to couple with other compounds, such as the R" and X groups, to form a starch derivative of formula (I), capable of selectively coupling with an active substance AND still maintaining the desirable degradability and controllable elimination behavior of the isolated and chemically unaltered HES compounds. Thus, it is clear that the described ranges do not pertain to HES compounds which are NOT chemically altered for coupling with other molecules to form such starch derivative.

Sommermeyer also teaches the use of hydroxyethyl starches prepared as described in EP 0 402724:

> *With the scope of this invention, used is preferably made of hydroxyethyl starches (HES) substituted predominantly in the C2 position, which are substituted as homogenously as possible. The preparation of such HES is described in EP 0 402724 B2. They are decomposable without residue within a physiologically reasonable period but on the other hand exhibit a controllable elimination behaviour. (Col. 3, lines 51-38, emphasis added)*

Thus, Sommermeyer explicitly teaches that the hydroxyethyl starches (HES) prepared as described in the EP '724 reference, "substituted predominantly in the C2 position, which are substituted as homogenously as possible", satisfy the criterion sought after for the starch derivative of formula (I), namely "they are decomposable without residue within a physiologically reasonable period but on the other hand exhibit a controllable elimination behavior". It should be noted that in contrast to the "hydroxyethyl radical within the formula (I)", which as described has been chemically altered (i.e., oxidized) to bind to other compounds to form the starch derivative of formula (I), the HES prepared by the cited EP '724 reference are isolated HES compounds which have not been chemically altered to bind to another compound.

Sommermeyer also makes clear that "the predominant C2 substitution" is essential for the "controllable elimination behavior" of the HES.

Specifically, the EP '724 reference (alternatively referred to as the '108 Sommermeyer reference) teaches a process for preparing a HES having a mean Molecular weight of 60-600,000, a molar substitution of 0.15-0.5 and a C2/C6 ratio of 8 to 20 ('108 Sommermeyer, Abstract, Col. 5, lines 45-50, emphasis added). The EP '724 patent teaches the preparation of a specific HES of average molecular weight 234,000 having a molar substitution MS 0f 0.24 and a C2/C6 ratio of 9.34 ('108 Sommermeyer, lines 18-20). Consistent with the teachings of the '661 Sommermeyer reference, EP '724 emphasizes that the high C2/C6 ratio is essential for providing the HES with a complete degradability but controllable elimination behavior, as further explained below:

> *The objective of the present invention, that is the preparation of a hydroxyethylstarch which can be completely broken down within a physiologically reasonable period and which on the other hand nevertheless has a controllable elimination behavior, is achieved by a starch substituted predominantly in 2-position and substituted as homogenously as possible. ('108' Sommermeyer, Col. 3, lines 25-30, emphasis added)*
>
> *The predominant 2-substitution makes the hydroxyethyl starch relatively difficult to degrade for α-amylase. ('108 Sommermeyer, Col. 3, lines 29-30, lines 33-35)*
>
> *It has been found that hydroxyethyl starches substituted extremely low (MS<0.5) and having a high ratio of the substitution of C2 to the substitution of C6 ([C2/C6 of 8 to 20]) . . . are rapidly and completely eliminated from the human body within the first hours of the infusion" ('108 Sommermeyer, Col. 3, lines 50-54, emphasis added).*
>
> *. . . [Furthermore, they] do have an adequately high solubility in aqueous medium so that the solutions are stable even for relatively long periods of time and do not form any agglomeration or gels which would make the further use as plasma expander solution impossible. (108' Sommermeyer, Col. 3, lines 56-62).*

Thus, the EP '724 reference teaches that a high C2/C6 ratio of from 8 to 20 is essential in providing HES with the desired properties, a complete degradability but controllable elimination behavior.

It should also be noted that even though the '661 reference teaches a "HES radical within the formula (I)" having characteristics which are different from those of the HES compounds taught by the cited EP '724 reference, there is no disclosure or suggestion in the '661 patent that the characteristics of the "hydroxyethyl starch radical within the formula (I)", such as for example a C2/C6 ratio from 2 to 12, would be desirable or suitable for an isolated HES compound. Thus, it is clear that the characteristics disclosed for the "oxidized HES radical within the formula (I)" are exclusive for an HES chemically altered for forming the starch derivative of formula (I) capable of selectively coupling to active substances, and STILL maintaining the desirable degradability and controllable elimination behavior of the chemically unaltered HES compounds as taught by the cited EP '724 reference.

In view of the foregoing description of the cited reference and as further discussed below, Applicant respectfully submits that the '661 Sommermeyer reference does not render claim 1 obvious for at least the following reasons:

1. The '661 Sommermeyer reference fails to disclose or suggest all the elements and limitations of claim 1.
2. From the teachings of the cited prior art, one of ordinary skill in the art would not have been motivated to modify the referenced HES to arrive at the claimed compound, since the cited reference actually teaches away from the claimed hydroxyethyl starch.
3. The Examiner failed to provide an articulated reason with rational underpinning as to why one of ordinary skill in the art would have <u>selectively</u> ignored the teachings of an unmodified and uncoupled HES for use as a plasma expander and instead would have <u>selectively</u> chosen to modify the "HES radical within the formula (I)" to arrive at the claimed hydroxyethyl starch for use as a plasma expander.

1. <u>The '661 Sommermeyer reference fails to disclose or suggest all the elements and limitations of claim 1</u>

"[O]bviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

As set forth above, the '661 Sommermeyer reference cites the EP '724 reference to disclose HES having a high C2/C6 ratio "which are decomposable without residue within a physiologically reasonable period and exhibiting a controllable elimination behavior". The EP '724 specifically teaches a C2/C6 ratio of 8 to 20. Thus, the '661 Sommermeyer does not disclose or suggest the HES of claim 1, which recites among other things a C2/C6 ratio of from 2 to below 8.

The '661 Sommermeyer reference also discloses a "hydroxyethyl starch (HES) radical" chemically altered to couple with other compounds, such as the R" and X groups, to form a starch derivative of formula (I), capable of selectively binding to an active substance AND STILL "are decomposable without residue within a physiologically reasonable period and exhibiting a controllable elimination behavior". By consistently and specifically referring to "a hydroxyethyl starch radical within the formula (I) to distinguish it from a chemically unaltered HES, such as the one prepared as described in the EP '724 reference, Sommermeyer makes clear that the characteristics disclosed for the "HES radical within the formula (I)" are specific for a HES which is chemically altered for coupling with other compounds (such as the X and R" groups) to form a starch derivative of formula (I) capable of selectively binding to active substances and still maintaining the desirable degradability and elimination behavior of an isolated and chemically unaltered HES. Thus, Sommermeyer makes it clear that the "HES radical within the formula (I)" is distinct from the HES prepared by the EP '724 reference. It is also clear that the characteristics of the "HES radical within the formula (I)" are <u>not</u> attributable to hydroxyethylstarches compounds intended for other purposes, such as, for example, for use as a volume replacement or plasma expander. Thus, the '661 Sommermeyer reference does not disclose the HES of claim 1, for use as a plasma expander or volume replacement, having an average molecular weight of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C2/C6 ratio of from 2 to below 8.

In summary, Applicant respectfully submits that: (1) Sommermeyer's "HES radical within the formula (I)" - chemically altered for coupling with other compounds to form a starch derivative capable of selectively binding to an active substance - is clearly distinct from a HES for use as a volume replacement or plasma extender; and (2) Sommermeyer's HES prepared as described by the EP '724 patent comprising a high C2/C6 ratio of 8 to 20 does not render the claimed hydroxyethyl starch obvious. Among other things, at a minimum, the '661 Sommermeyer reference and its cited EP '724 reference do not disclose or suggest a hydroxyethyl starch for use as a volume replacement or plasma expander having an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8, as recited by claim 1.

2. From the teachings of the cited prior art, one of ordinary skill in the art would not have been motivated to modify the referenced HES radical to arrive at the claimed compound, since the cited references teach away from the claimed hydroxylethyl starch.

"[T]he test [for obviousness] is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In Sovich*, 769 F. 2d at 742-43.

As set forth above, the '661 Sommermeyer patent cites the EP '724 reference to disclose a HES, having a high C2/C6 ratio, of from 8 to 20, which can be completely broken down within a physiologically reasonable period and which on the other hand nevertheless has a controllable elimination behavior. The '661 Sommermeyer also teaches a HES radical chemically altered to couple with other compounds to form a starch derivative of formula (I).

Both the'661 Sommermeyer reference and its cited EP '724 reference would have disclosed to one of ordinary skill in the art that a HES, which can be used as a plasma expander or volume replacement, should have a high C2/C6 ratio (from 8 to 20) to achieve the described properties. Therefore, from the teachings of the cited references, a skilled artisan would have been taught away from the claimed HES, which recites among other things, a hydroxyethyl starch for use as a volume replacement or plasma expander characterized by having a C2/C6

ratio of from 2 to below 8, which is clearly below the range taught by the EP '724 reference. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant". In *re Gurley*, 27 F. 3d 551, 553 (Fed. Cir. 1994). Therefore, contrary to the Examiner's assertion, Applicant respectfully submits that a skilled artisan would not have been motivated to modify the cited reference to produce the claimed hydroxyethyl starch.

3. The Examiner fails to provide an articulated reason with rational underpinning as to why one of ordinary skill in the art would have selectively ignored the teachings of a chemically unaltered HES, for use as a plasma expander, and instead would have selectively chosen to modify the "HES radical within the formula (I)", chemically altered for forming an intermediate starch derivative capable of selectively binding to an active substance, to arrive at the claimed hydroxyethyl starch for use as a plasma expander.

In rejecting claims under 35 U.S.C. § 103(a), the Examiner bears the initial burden of establishing a *prima facie* case of obviousness. *In re Piasecki,* 745 F.2d 1468, 1471-72, 223 USPQ 785, 787-87 (Fed. Cir. 1984).

In rejecting the pending claims as being unpatentable over the '661 Sommermeyer reference, the Examiner merely states:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the conjugates and compositions of Sommermeyer et al having the molecular weight, degree of substitution, and C2/C6 ratio recited in the instant claims. The claimed ranges overlap or fall within the ranges disclosed in the prior art. One of ordinary skill would have been able to arrive at the claimed ranges through a process of optimizing these results-effective variables within the broad disclosure of the prior art. (Office Action, page 11)

As set forth above, the '661 Sommermeyer patent teaches a HES radical which is chemically altered to bind to other compounds (R" and X groups) to form a starch derivative

capable of selectively binding to an active substance. Applicant respectfully submits that the Examiner has not adequately explained why one of ordinary skill in the art would have been led to modify the chemically altered "HES radical within the formula (I)" taught by Sommermeyer to produce the claimed HES. The Examiner has not cited disclosure in the cited reference or provided a convincing line of reasoning to support his assertion that a skilled artisan would have been motivated to chemically break the HES radical from its bound partners, then reduce it, and subject it to further chemical modifications to obtain the claimed HES for use as a plasma expander or volume replacement. For that matter, the Examiner has not set forth the level of ordinary skill in the art as required by *Graham et al. v. John Deere Co.*

For chemical cases, "[i]n determining whether a case of *prima facie* obviousness exists, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the claimed substitution or other modification". In *re Taborsky*, 502 F.2d 775, 780, 183 U.S.P.Q. (BNA) 50, 55 (CCPA 1974). The prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound. In *re Stemniski*, 58 C.C.P.A. 1410, 444 F.2d 581, 586, 170 U.S.P.Q. (BNA), 343, 347 (CCPA 1971).

Furthermore, as set forth above, Sommermeyer also discloses hydroxyethyl starches (HES) prepared as described in EP 0 402724, which unlike the "HES radical within the formula (I)", are not chemically altered to bind to other compounds, and which can be used as a plasma explander in volume substitution or hemodilution. The Examiner has failed to explain why and how a skill artisan would have selectively ignored Sommermeyer's teachings of a HES compound, - chemically unaltered, proven to possess a complete degradability and controllable elimination behavior, usable as plasma expander in volume substitution and hemodilution -, and instead would have selectively chosen to modify the "HES radical within the formula (I)", - chemically altered for binding other compounds to form an intermediate starch derivative capable of selectively binding to an active substance -, to arrive at the claimed HES compound.

"A prior art reference must be considered in its entirely, i.e., as a whole, including portions that would lead away from the claimed invention" (§ MPEP 2141.02 (VI)). Applicant

respectfully submits that the Examiner's selective reliance on the properties of the "HES radical within the formula (I)" to reject the pending claims is merely an attempt at impermissible hindsight. It is improper to base a conclusion of obviousness upon facts gleaned only through hindsight. "To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction – an illogical and inappropriate process by which to determine patentability." Sensonic, Inc. v. Aerosonic Corp. 81 F.3d 1566, 1570 (Fed Cir. 1996). "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made." Id

In view of the foregoing, Applicant respectfully submits that the Examiner has failed to set forth the Graham factors and failed to articulate a reason with rational underpinning to support the legal conclusion as to why a skilled artisan would have modified the cited reference to arrive at the claimed compound. "Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness" *KSR Int'l v. Teleflex, Inc.* 550 U.S. 398, 417 (2007) (quoting *In re Kahn,* 441 F.3d 977, 988 (Fed. Cir. 2006)). As such, the Examiner has failed to establish a *prima facie* case of obviousness.

For at least the reasons set forth above, Applicant respectfully submits that the rejection of claim 1 under § 103(a) cannot be properly maintained. Claims 24-33 depend either directly or indirectly from claim 1, and therefore they too are allowable for the same reasons.

Of the rejected claims, amended independent claim 34 recites:

> 34. (Currently Amended) A pharmaceutical formulation for use in at least one of maintaining normovolemia, improving macro and microcirculation, improving nutritive oxygen supply, stabilizing hemodynamics, improving volume efficiency, reducing plasma viscosity, increasing anemia tolerance, and performing hemodilution, the pharmaceutical formulation comprising a hydroxyethylstarch comprising an-average molecular weight, Mw, of greater than or equal to 500,000, a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8.

Claim 34 is directed to a pharmaceutical formulation for use in, among other things, maintaining normovolemia, improving volume efficiency, performing hemodilution. The pharmaceutical formulation recited by claim 34 comprises a hydroxyethylstarch having an average molecular weight of greater than or equal to 500,000 and a C2/C6 ratio of from 2 to below 8.

As set forth above, the '661 Sommermeyer does not disclose or suggest a hydroxyethyl starch for use in volume substitution or hemodilution comprising, among other things, a C2/C6 ratio of from 2 to below 8. The '661 Sommermeyer also does not disclose or suggest a pharmaceutical formulation for use in volume replacement to maintain normovolemia or in performing hemodilution. Thus, the '661 Sommermeyer fails to render claim 34 obvious under §103(a). Among other things, at a minimum, the '661 Sommermeyer reference does not disclose or suggest a pharmaceutical formulation comprising a hydroxyethyl starch having an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8, as recited by claim 34.

Furthermore, by teaching that a high C2/C6 ratio (from 8 to 20, '108 Sommermeyer, Abstract) is essential for providing the HES with a complete degradability but controllable elimination behavior ('661 Sommermeyer, Col. 3, lines 55-58), the cited EP '724 reference teaches away from the claimed formulation, which among other things, recites a hydroxyethyl starch comprising a C2/C6 ratio of from 2 to below 8.

Furthermore, the Examiner has failed to provide an articulated reasoning with some rationing underpinning as to why or how a skilled artisan would have found the claimed limitations obvious in view of the teachings of the cited references. For at least the reasons set forth above, Applicant respectfully submits that the rejection of claim 34 under § 103(a) cannot be properly maintained. Claims 42 and 43 depend from claim 34, and therefore they too are allowable for at least the same reasons.

Although dependent claim 42 is patentable due to its dependency on claim 34, it is further independently patentable over the cited reference for additional reasons. Among other things, claim 42 further modifies claim 34 and specifies that the pharmaceutical formulation is characterized by being a volume replacement.

As set forth above, the EP '724 reference, cited by the '661 Sommermeyer patent, specifically teaches a hydroxyethyl starch for use as a plasma expander in volume substitution and hemodilution, characterized by having a high C2/C6 ratio of from 8 to 20. Thus, not only do the cited references fail to disclose or suggest all the claimed elements and limitations, they teach away from the claimed formulation. Thus, claim 42 is independently patentable over the cited references.

Of the rejected claims, previously presented independent claim 52 recites:

> 52. (Previously Presented) A method of preparing a plasma replacement or plasma expander, said method comprising the step of preparing a pharmaceutical formulation comprising a hydroxyethylstarch comprising an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8.

Claim 52 recites a method of preparing a plasma replacement or plasma expander, comprising the step of preparing a pharmaceutical formulation comprising a hydroxyethylstarch, comprising, among other things, an average molecular weight of greater than or equal to 500,000 and a C2/C6 ratio of from 2 to below 8. Thus, similarly to claim 1, the hydroxyethylstarch of claim 52 is used as a plasma replacement or plasma expander.

As set forth above, the '661 Sommermeyer reference does not disclose or suggest a hydroxyethyl starch for use as a plasma expander in volume substitution or hemodilution comprising, among other things, a C2/C6 ratio of from 2 to below 8. The '661 Sommermeyer reference also does not disclose or suggest a method of preparing a plasma replacement or plasma expander, comprising the step of preparing a pharmaceutical formulation comprising a hydroxyethylstarch comprising an average molecular weight, Mw, of greater than or equal to

500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8, as recited by claim 52.

Furthermore, by teaching that a high C2/C6 ratio (from 8 to 20, '108 Sommermeyer, Abstract) is essential for providing the HES with a complete degradability but controllable elimination behavior ('661 Sommermeyer, Col. 3, lines 55-58), the cited EP '724 reference teaches away from the claimed method, which among other things, recites a hydroxyethyl starch comprising a C2/C6 ratio of from 2 to below 8.

Furthermore, the Examiner has failed to provide an articulated reasoning with some rationing underpinning as to why or how a skilled artisan would have found the claimed limitations obvious in view of the teachings of the cited references. For at least the reasons set forth above, Applicant respectfully submits that the rejection of claim 52 under § 103(a) cannot be properly maintained.

Claims 60 and 61 depend from claim 52, and therefore are also allowable for at least the same reasons.

§ 103(a) Rejection of 62-69 by the '601 Sommermeyer reference in view of the '108 Sommermeyer

In rejecting claims 62-69 as being unpatentable over the '661 Sommermeyer reference in view of the '108 Sommermeyer patent, the Examiner contends that the '661 Sommermeyer reference discloses the claimed hydroxyethyl starch but does not disclose a process of making the claimed starch. The Examiner relies on the '108 Sommermeyer reference to disclose a method of making a method of preparing a hydroxyethyl starch as claimed. The '108 Sommermeyer reference discloses a process for making a hydroxyethyl starch. The Examiner concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to use the process of '182 [sic] to make a hydroxyethylstarch for use in the invention of Sommermeyer et al. One of ordinary skill in the art would have been motivated to make this starch because Sommermeyr et al. renders obvious a starch having the claimed properties as discussed above. One of ordinary skill in the art would have reasonably expected success because Sommermeyer et al. specifically refers to the

priority application of the '182 [sic] as teaching a method of making the disclosed starches. (Office Action, pages 12-13)

The '108 Sommermeyer patent actually corresponds to the cited EP '724 reference, which was discussed above.

Of the rejected claims, independent claim 62 recites:

62. (Previously Presented) A process for preparing a hydroxyethylstarch comprising the steps:

(i) reacting water-suspended starch with ethylene oxide; and

(ii) partially hydrolyzing a starch derivative with acid until a desired range of average molecular weight of the hydroxyethylstarch is reached; and

wherein the hydroxyethylstarch comprises an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8.

As set forth above, the '661 Sommermeyer patent specifically teaches a "HES radical within the formula (I)" chemically altered to bind to other compounds for forming an intermediate starch derivative capable of selectively binding to an active substance. Thus, the disclosed characteristics are consistently and specifically attributable to the chemically altered "HES radical within the formula (I)" and not to isolated HES compounds which are chemically unaltered for binding to other compounds. Thus, the '661 does not disclose the claimed HES or a method for preparing the claimed HES.

As set forth above, the cited '724 patent or the '108 patent specifically teaches a HES, and a method for making such a HES, having a mean Molecular weight of 60-600,000, a molar substitution of 0.15-0.5 and a ratio of the substitution of C2 to the substitution of C6 (C2/C6) of 8 to 20 ('108 Sommermeyer, Abstract). The '108 Sommermeyer patent teaches that a high C2/C6 ratio is essential in providing the HES with the ability to be "decomposable without residue within a physiologically reasonable period but on the other hand exhibit a controllable elimination behavior" (661 Sommermeyer, Col. 3, lines 55-58). Thus, the '108 patent does not disclose the claimed method. At a minimum, the cited references do not disclose or suggest a

method for preparing a hydroxyethyl starch wherein the hydroxyethylstarch comprises, among other things, a C2/C6 ratio of from 2 to below 8.

Furthermore, by specifically teaching that a high C2/C6 ratio from 8 to 20 is required to achieve the desired properties, the '108 Sommermeyer teaches away from the claimed method. Therefore, one of ordinary skill in the art would not have been motivated to modify the cited references to arrive at the claimed method.

For at least the reasons set forth above, Applicant respectfully submits that the cited references fail to render claim 62 obvious under § 103(a). Since claims 63-69 depend from claim 62, they are also allowable over the cited references for at least the same reasons.

§ 103(a) Rejection of Claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57, 79-84, and 86-87 by Sommermeyer in view of Lederman et al.

In rejecting claims 35, 37-39, 41, 45-47, 49-51, 53, 55-57, 79-84 and 86-87 as being unpatentable over the '661 Sommermeyer reference in view of the '294 Lederman reference, the Examiner contends that the '661 Sommermeyer reference discloses the claimed hydroxyethyl starch; however Sommermeyer does not disclose a composition or kit comprising a sterile aqueous solution of hydroxyethylstarch or a monoclonal antibody. The '294 Lederman reference discloses antibodies and a pharmaceutical composition comprising a monoclonal antibody and a pharmaceutically acceptable carrier, including phosphate buffered saline. The Examiner concludes:

> It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the antibodies of Lederamn et al as starch conjugates as described by Sommermeyer et al. and to include these conjugates in a sterile solution of phosphate buffered saline. . . . One of ordinary skill in the art would have been motivated to do so because Sommermeyr et al. discloses that the disclosed hydroxyethyl starches can be conjugated to antibodies to improve their therapeutic properties. One of ordinary skill in the art would reasonably have expected success because preparing a pharmaceutical composition of a known active ingredient is well known and routine in the art. (Office Action, pages 12-13).

Of the rejected claims, claims 35, 37-39, 41, 45-47, 49-51 depend from directly or indirectly from claim 34 and claims 53, 55-57 depend directly or indirectly from claim 52.

As set forth above, the '661 Sommermeyer reference fails to render independent claims 34 and 52 obvious for not disclosing all the elements of the claimed methods. Furthermore, the cited EP'724 reference teaches away from the claimed methods by teaching that a high ratio of C2/C6 (from 8 to 20) is essential in providing the HES with the ability to "be decomposable without residue within a physiologically reasonable period but on the other hand exhibit a controllable elimination behavior" (661 Sommermeyer, Col. 3, lines 55-58). Therefore, one of ordinary skill in the art would not have been motivated to modify the chemically altered HES radical disclosed by the 661' Sommermeyer patent to arrive at the claimed methods.

Furthermore, the Examiner failed to establish a *prima facie* case of obviousness for failing to provide an articulated reason with rational underpinning as to why from the teachings of the cited prior art a skilled artisan would have been led to selectively modify the chemically altered "HES radical within the formula (I)" to produce the claimed method. As Lederman is merely relied on to disclose a pharmaceutical composition comprising a monoclonal antibody and an acceptable carrier, it does not cure the deficiencies of Sommermeyer.

Even if combinable, a position that Applicant does not concede, the combination of Sommermeyer and Lederman still fails to render claims 34 and 52 obvious under § 103(a). As claims 35, 37-39, 41, 45-47, 49-51 depend from directly or indirectly from claim 34 and claims 53, 55-57 depend directly or indirectly from claim 52, they too are allowable for at least the same reasons.

Of the rejected claims, previously presented independent claim 79 recites:

79. (Previously Presented) A kit comprising separately:
(i) a hydroxyethylstarch; and
(ii) a sterile salt solution

wherein the hydroxyethylstarch comprises an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C_2/C_6 ratio of from 2 to below 8.

As set forth above, the '661 Sommermeyer patent does not disclose or suggest a hydroxyethyl starch comprising, among other things, a C2/C6 ratio of from 2 to below 8. The '661 Sommermeyer also does not disclose or suggest a kit comprising a hydroxyethyl starch comprising, among other things, a C2/C6 ratio of from 2 to below 8.

Furthermore, by teaching that a high C2/C6 ratio (from 8 to 20, '108 Sommermeyer, Abstract) is essential for providing the HES with a complete degradability but controllable elimination behavior ('661 Sommermeyer, Col. 3, lines 55-58), the '661 Sommermeyer reference actually teaches away from the claimed kit, which among other things, recites a hydroxyethyl starch comprising a C2/C6 ratio of from 2 to below 8. As Lederman is merely relied on to disclose a pharmaceutical composition comprising a monoclonal antibody and an acceptable carrier, it does not cure the deficiencies of Sommermeyer.

Even if combinable, a position that Applicant does not concede, the combination of Sommermeyer and Lederman still fails to render claim 79 obvious under § 103(a). At a minimum, the cited references do not disclose or suggest a kit comprising separately a hydroxyethyl starch and a sterile salt solution, wherein the hydroxyethylstarch comprises an average molecular weight, Mw, of greater than or equal to 500,000, characterized by having a molar substitution MS of from 0.25 to 0.5 and a C2/C6 ratio of from 2 to below 8, as recited in claim 79. Claims 80 to 84 and 86 to 87 depend directly or indirectly from claim 79, therefore they are also allowable over the cited references.

§ 103(a) Rejection of Claim 59 over Sommermeyer in view of Lederman and further in view of Haisma

In rejecting claim 59 as being unpatentable over Sommermeyer in view of Lederman and further in view of Haisma, the Examiner contends that Sommermeyer in view of Lederman discloses the method as recited by claim 52, except for the step of filtrating and sterilizing the hydroxyethyl starch. The Examiner relies on Haisma for disclosing the missing step.

Claim 59 depends from claim 52. As set forth above, the combination of Sommermeyer in view of Lederman, even if combinable, still fails to render claim 52 for not disclosing all the

claimed elements and limitations. Furthermore, by teaching that a high C2/C6 ratio (from 8 to 20, '108 Sommermeyer, Abstract) is essential for providing the HES with a complete degradability but controllable elimination behavior ('661 Sommermeyer, Col. 3, lines 55-58), the cited EP '724 reference teaches away from the claimed method. As Haisma is merely relied on to disclose the filtrating and sterilizing steps, it does not make up the deficiencies of Sommermeyer and Lederman. Even if combinable, a position that Applicant does not concede, the references still fail to disclose all the elements and limitations of claim 52 and thus fails to render claim 52 obvious under § 103(a). As claim 59 depends from claim 52, it too is allowable for at least the same reasons.

CONCLUSION

In view of the amendments and the remarks set forth above, the application is thought to be in condition for allowance.

Should the Examiner find it necessary to speak with Applicant's attorney, he is invited to contact the undersigned at the telephone number indicated below.

Respectfully submitted,
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